PATENT
Customer No. 23517
Attorney Docket No. 19124.0002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Barry N. KREISWIRTH et al.	)	Group Art Unit: 1631
	)	
Application No.: 09/656,084	)	Examiner: Cheyne D. Ly
	)	
Filed: September 6, 2000	)	
	)	
For: SYSTEM AND METHOD FOR TRACKING AND CONTROLLING INFECTIONS	)	Confirmation No.: 8869

Attention: Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

In support of the Notice of Appeal filed June 28, 2005, and further to Board Rule 41.37, Appellants present this brief and enclose herewith a check for the fee of $250.00 required under 37 C.F.R. § 41.20(b)(2) for a small-entity together with a Petition for Extension of Time extending the time for response to November 28, 2005.

This Appeal responds to the March 28, 2005, final rejection of claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44. If any additional fees are required or if the enclosed payment is insufficient, Appellants request that the required fees be charged to Deposit Account No. 19-5127 (Order No. 19124.0002).

Table of Contents

I. Real Party In Interest

eGenomics is the assignee of record, as evidenced by the assignment document filed in the U.S. Patent and Trademark Office on December 20, 2000, and recorded at Reel 011405 and Frame 0291.

II. Related Appeals and Interferences

There are currently no other appeals or interferences, of which Appellants or Appellants' legal representative are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44 stand finally rejected under 35 U.S.C. § 103(a) and are appealed by Appellants. Claims 2, 6, 9, 15, 18-20, 27, and 39-41 have been canceled. Claims 42-43 are subject to a restriction requirement and have been withdrawn. A list of the appealed claims is presented in the attached Appendix A. No claims have been allowed.

IV. Status Of Amendments

No claim amendments have been made in response to or subsequent to the final Office Action dated March 28, 2005.

V. Summary Of Claimed Subject Matter

a. Overview

The spread of drug-resistant and virulent strains of bacteria in hospitals and health care facilities is a significant problem. (*See, e.g.*, Applicant's Specification, Background at p. 1, l. 6 to p. 4, l. 11.) One conventional method that is used by hospitals to identify a particular strain of bacteria is pulsed-field gel electrophoresis (PFGE). The gel electrophoresis process involves cutting bacterial DNA into multiple micro-fragments of varying sizes and molecular weights, and producing a photographic image containing a pattern indicative of the respective weights of the fragmented bacterial DNA. A strain of bacteria is identified by comparing gel electrophoresis photographic images. (*See id.* at p. 5, l. 20 to p. 6, l. 3.) This method of subspeciating bacteria suffers from a number of problems that makes it ill-suited for use on a computerized system. For example, gel electrophoresis images can fail to show differences between two related bacterial DNA isolates and the images are not convenient for storing in a database. In addition, it is difficult to compare and analyze the resulting photographic image data. Furthermore, such methods are incapable of determining DNA sequence. (*See id.* at p. 6, ll. 4 – 19.) The present invention, as recited in the claims described below, introduces a novel computerized system and method for tracking the spread of infectious organisms by analyzing the DNA sequence data (*i.e.*, the sequence of nucleotides, A's, G's, C's, and T's) of the VNTR (variable number of tandem repeats) regions of bacterial isolates rather than performing conventional analysis of pulsed-field gel images.

b. Claim 1

Independent claim 1 is directed to a method of tracking spread of infectious bacteria. The invention of claim 1 includes obtaining a plurality of bacterium samples from a plurality of patients or objects at a plurality of different physical locations. (*See, e.g.*, Applicants' specification at p. 17, ll. 3-4; p. 17, l. 14 - p. 18, l. 6, p. 18, ll. 10-12; FIG. 2A (Step 204).) A first region of DNA is sequenced from each bacterium sample, wherein the first region consists essentially of a variable number of tandem repeats (VNTR) region. (*See, e.g., id.* at p. 8, ll. 4-5; p. 14, ll. 3-5; p. 18, l. 13-14; p. 19, l. 12 – p. 23, l. 11; Fig. 2A (Step 216).)

As the name indicates, a VNTR region is a region of the DNA comprised of a variable number of repeats that are "in tandem"—*i.e.*, adjacent. Studies performed by the inventors of the present invention have shown sequencing of VNTR regions to be an effective rapid typing tool for use in epidemiological tracking of infectious organisms. (*See, e.g., id.* at p. 21, l. 11 to p. 23, ll. 11; p. 8, ll. 17-21.)

The sequence data from the first sequenced region is stored in a database for each of the plurality of bacterium samples. (*See, e.g., id.* at page 13, ll. 16-17, p. 14, ll. 1-5; p. 16, ll. 1-8; p. 24, ll. 9-11; FIG. 1 (items 130, 103, 111, 115); FIG. 2A (Step 222).) A physical location of the patient or object from which each bacterium sample was obtained is also stored in the database. (*See, e.g., id.* at p.18, ll. 6-12.)

The sequence data stored in the database of at least two of the plurality of samples are compared and a measure of the phylogenetic relatedness between the compared samples is determined based on the compared sequence data. (*See, e.g.,*

id. at p. 24, ll. 19-21.) In other words, the similarity of two sequences of DNA is indicative of the phylogenetic relatedness of the two isolates.

The comparison of the sequence data is performed on both a base pair level and a repeat motif level. (*See, e.g., id.* at p. 24, ll. 19-21.) A "repeat sequence" is a repeating sequence of nucleotides and is also called a "cassette." (*See id.*, p. 28, l. 15 – p. 29, l. 11.) A "repeat motif" is a pattern of cassettes. (*See id.*, p. 29, l. 11-12.) Comparison of two strands of DNA on a repeat motif level is performed by comparing the pattern of cassettes present in each strand of DNA. (*See id.*, p. 31, l. 5 to p. 32- l. 4; FIG. 3 (step 308).) Comparison of two strands of DNA on a base pair level is performed by comparing the sequence of individual base-pair nucleotides (i.e., A's, G's, C's, and T's) rather than pattern of cassettes. (*See, e.g., id.* at p. 32 at ll. 9-11; FIG. 3 (step 310).) An example of an equation is given on page 32 of Applicants specification for determining a "cost" (a measure of phylogenetic relatedness) between two strands of DNA based on a comparison of the DNA sequence data at both the repeat motif level and at the base pair level. (*See, e.g, id.* at p. 32, ll. 12 – p. 33, l. 20.)

After the DNA has been compared and a phylogenetic relatedness determination is made, patients infected or objects contaminated with phylogenetically related bacteria are identified based on the phylogenetic relatedness determination. The spread of the bacteria is then tracked based on: a) the identified patients or contaminated objects, and b) the physical locations of the identified patients or objects stored in the database. (*See, e.g., id.* at p. 25, l. 6 – p. 26, l. 13; p. 27, ll. 15-21; FIG. 2B (Step 227); FIG. 3 (Step 318).) A warning is then provided based on the tracking of the spread of the bacteria wherein the warning allows the recipient of the warning to control the further

spread of the bacteria. (*See, e.g., id.* at p. 27 l. 20 – p. 28, l. 2; p. 28, ll. 10-14; FIG. 2B (Step 230).)

c. Claim 16

Claim 16 depends from claim 1 and recites a feature of the invention that allows a VNTR region of the DNA to be most effectively analyzed. Specifically, the invention of claim 16 identifies repeat sequences (also called cassettes) in the sequence data for each of the compared samples. (*See, e.g.*, Applicants' specification at p. 28, l. 15 – p. 29, l. 24.) The invention then recognizes that repeat regions of bacterial DNA sometimes mutate by the insertion and/or deletion of whole cassettes. (*See, e.g., id.* at p. 31, ll. 1-3.) For example, a single 24 base pair cassette can be inserted or deleted by a single event. (*See, e.g., id.* at p. 31, ll. 4-5.) The invention recited in claim 16 treats the insertion or deletion of a cassette as a single event. For example, the software of the invention recognizes the insertion or deletion of a single 24 base-pair length cassette as a single event, rather than 24 separate events. (*See, e.g., id.* at p. 31, l. 5 - p. 32, l. 4; p. 34, l. 19 - p. 35, l. 11.) This allows the software of the invention to effectively analyze a VNTR region of the bacterial DNA.

d. Claim 32

Independent claim 32 is directed to a system for tracking spread of infectious bacteria. It includes a computer network, (*See, e.g.*, Applicants' Specification at p. 12, . ll. 4-6; FIG. 1(network 100)); a centralized database, (*See, e.g.*, Applicants' Specification at p. 13, ll. 16-22); and a remote facility connected to the computer

network, the remote facility obtaining a plurality of bacterium samples from a plurality of patients or objects at a plurality of different locations. (*See, e.g.*, Applicants' Specification at p. 11, l. 21 – p. 12, l. 3; p. 16, l. 16 – p. 18, l. 9.) The server performs a method similar to the method summarized in section a. above. (*See, e.g.*, Applicants' Specification at p. 16, ll. 16-17.)

e. Claim 33

Independent claim 33 is directed to computer executable software code stored on a computer readable medium for performing a method of tracking spread of infectious bacteria over a computer network. The method is similar to the method summarized in section a., above. (*See, e.g.*, Applicants' specification at p. 10, ll. 19-23; p. 13, ll. 8-10.)

VI. Grounds of Rejection

Claims 1, 3-5, 7, 8, 12-14, 16, 17, 21, 25-34, 36, and 44 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of the following three references:

(1) U.S. Patent No. 5,619,991A to Sloane ("*Sloane*");

(2) Hoe et al., "Rapid Molecular Genetic Subtyping of Serotype M1 Group A Streptococcus Strains," *Emerging Infection Diseases*, Vol. 5, No. 2, March-April 1999, pp. 254-262 ("*Hoe*"); and

(3) van Belkum et al., "Variable Number of Tandem Repeats in Clinical Strains of Haemophilus Influenzae," *Infection and Immunity*, Dec. 1997, pp. 5017-5027 ("*van Belkum*").

(*See* 3/28/05 Final Office Action at p. 3, ¶ 7.)

Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44 also stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of the following five references:

(1) *Sloane*;

(2) *Hoe*;

(3) *van Belkum*;

(4) O'Brien et al., Chest, 112:387-382 ("*O'Brien*"); and

(5) U.S. Patent No. 6,404,340 to Paradiso et al. ("*Paradiso*").

(*See* 3/28/05 Final Office Action at p. 16, ¶ 48.)

VII. Argument

The Rejections of Claims 1, 3-5, 7, 8, 12-14, 16, 17, 21, 25-34, 36, and 44 Under 35 U.S.C. § 103(a) Over the Combination of *Sloane*, *van Belkum*, and *Hoe* Should Be Reversed

To establish a prima facie case of obviousness, three basic criteria must be met. First, the prior art reference or references, taken alone or combined, must teach or suggest each and every element recited in the claims. *See* MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981(CCPA 1974); M.P.E.P. § 2143.03. Second, there must be some suggestion or motivation to combine the references in a manner resulting in the claimed invention. *See* M.P.E.P. § 2143.01; *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270 (Fed. Cir. 2004). Third, a reasonable expectation of success must exist. *See* M.P.E.P. § 2143.02, citing *In re Merck & Co., Inc.*, 800 F.2d 1091(Fed. Cir. 1986); M.P.E.P. § 2143.02. Moreover, "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure." M.P.E.P. 2143, citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); MPEP 2143. "It is insufficient to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985).

The Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness in connection with the rejections of claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44. Instead, the Examiner uses the Applicants' own specification as a blueprint to piece together various portions of three disparate references: *Sloane*, *van Belkum* and *Hoe*.

As explained in further detail below, the Examiner's rejection of these claims should be reversed for several reasons. First, neither *Sloane*, *van Belkum*, nor *Hoe* disclose or suggest sequencing a VNTR region or comparing the sequence data from such a region to perform infection tracking, as required by independent claims 1, 32 and 33. Second, neither *Sloane*, *van Belkum*, nor *Hoe* disclose or suggest comparing sequence data on both a base pair level and a repeat motif level, as required by independent claims 1, 32 and 33. Third, one of skill in the art would not have been motivated to combine the patient diagnosis system of *Sloane* with the gel electrophoresis photograph analysis disclosed by *van Belkum* with the spacer oligotyping method disclosed by *Hoe*. Fourth, neither *Sloane*, *van Belkum*, nor *Hoe* disclose or suggest treating the insertion or deletion of a repeat sequence as a single genetic event, as recited in claim 16. Thus, the Examiner's rejections should be reversed.

A. Neither *Sloane, van Belkum*, nor *Hoe* Discloses Sequencing a VNTR Region or Comparing the Sequence Data From Such a Region to Perform Tracking of the Spread of Bacteria As Required by Independent Claims 1, 32 and 33

The claimed invention is directed towards a system and method for tracking the spread of infectious bacteria by sequencing a *variable number of tandem repeats* (VNTR) region in the DNA for a plurality of bacterium samples and comparing the sequence data from such a region to determine the phylogenetic relatedness of the bacterial samples. As the name "VNTR" indicates, the repeats (also called cassettes) in such a region are variable in number and "in tandem"; *i.e.*, they are adjacent to each other. *See, e.g.*, American Heritage College Dictionary 1385 (3d ed. 2000) (defining

"tandem" as "an arrangement of two or more persons or objects placed one behind the other."); http://tandem.bu.edu/trf/trf.html ("A tandem repeat in DNA is two or more adjacent, approximate copies of a pattern of nucleotides.").) http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=genomes.glossary.9089 ("Tandemly repeated DNA" are "DNA sequence motifs that are repeated head to tail"; "Variable number of tandem repeats (VNTR)" are "[a] type of simple sequence length polymorphism comprising tandem copies of repeats that are a few tens of nucleotides in length."); http://www.web-books.com/MoBio/Free/Ch3G1.htm ("Tandem repeats are an array of consecutive repeats.")

Thus, a variable number of tandem repeats (VNTR) region in DNA is a region comprised of a variable number of adjacent, approximate copies of a pattern of nucleotides. Figures 4B and 5 of Applicants' specification depict examples of such regions composed of a variable number of adjacent, approximate copies of a pattern of nucleotides (repeats). Studies performed by the inventors of the present application have shown that sequencing such a region and comparing the sequence data provides an effective epidemiological tracking tool for use with a computerized tracking system. (*See, e.g.*, Applicants' specification at p. 21, l. 11 to p. 23, l. 11.) In contrast, as explained further below, none of the three references combined by the Examiner (*Sloane*, *van Belkum*, and *Hoe*) disclose sequencing a VNTR region, as required by independent claims 1, 32 and 33. Moreover, none of these references discloses comparing the sequence data from a VNTR region to perform computerized tracking of the spread of bacteria, as required by independent claims 1, 32 and 33. Thus, for this reason alone the Examiner has failed to establish a *prima facie* case of obviousness.

1. *Sloane*

In contrast to the claimed invention, which is directed to tracking the spread of infectious bacteria by analyzing bacterial DNA, *Sloane* discloses a computerized system for diagnosing and treating patients using electronic data communications. (*Sloane*, Abstract, ll. 1-10.) According to *Sloane*, a patient initiates an electronic data call to an "e-doc" (electronic doctor) computer which executes a software-based medical expert system. (*Id.*, col. 3, ll. 48-54 & col. 4, ll. 3-5) The e-doc computer prompts the caller for symptoms and then arrives at a diagnosis for what ails the patient. (*Id.*, col. 4, ll. 5-9.) Once the interaction with the medical expert system has been completed, a second, epidemiological expert system is invoked. (*Id.*, col. 4, ll. 28-30.) The epidemiological expert system may ask the caller whether he/she has traveled recently and, if so, to where and when; the name of the cruise ship on which the caller may have traveled during the trip; the name of any professional meeting or conference that may have been attended; etc. (*Id.*, col. 4, ll. 34-40.) This data can be sent to a computer at the CDC, which can "provide a diagnosis based on an epidemiological phenomena." (*Id.*, col. 4, line 41-44 & col. 5, ll. 40-47) For example, the CDC can determine whether the "patient's symptoms are consistent with diagnoses that have already been confirmed for other patients in the patient 11's geographical area , *e.g.* an outbreak of food poisoning in the local area." (*Id.*, col. 5, ll. 47-52.)

Sloane also discloses that the CDC computer can execute a plurality of processes 84 that monitor the entire database of patient transaction records "looking for the known signatures of particular respective diseases." (*Id.*, col. 8, ll. 2-8.) By so monitoring, the "CDC is in a better position to carry out its charter of reporting and/or

suggesting treatment modalities for such diseases." (*Id.*, col. 8, ll. 9-12.) For example, *Sloane* discloses that the CDC can identify if a number of patients have been diagnosed with food poisoning in the same geographical location. (*Id.*, col. 8, ll. 15-18.)

The Examiner acknowledges that "Sloane does not describe the limitation of tracking spread of bacteria by sequencing a first region comprising the VNTR sequences." (3/28/05 Final Office Action at p. 12, ¶ 31.) In fact, *Sloane* does not disclose any sequencing of bacterial DNA. *Sloane* does not even mention or suggest DNA or DNA analysis. Nor does *Sloane* mention or suggest tracking the spread of bacteria. At best, *Sloane* discloses that the CDC can identify the existence of a number of reported similar diagnoses such as food poisoning in the same geographical location. (*Sloane*, col. 8, lines 2-18.) But *Sloane* does not disclose any tracking of the spread of bacteria, or any type of analysis that would allow *Sloane's* system to track the spread of bacteria.

Nevertheless, the Examiner relies on *van Belkum* and *Hoe* to cure these deficiencies in *Sloane*. (3/28/05 Final Office Action at pp. 12-16.) Applicants respectfully submit, however, that neither *Hoe* nor *van Belkum* cure the deficiencies in *Sloane* because, as described in further detail below, neither of these references discloses sequencing a VNTR region or comparing sequenced data from a VNTR region to perform a method of tracking the spread of infectious bacteria, as required by claim 1. Furthermore, none of the cited references discloses comparing sequence data on both a repeat motif and a base pair level, as recited in claim 1. Moreover, there is no motivation to combine these references.

2. *van Belkum*

van Belkum performs gel electrophoresis of *H. influenzae* isolates and analyzes the resulting ***gel electrophoresis photographs*** to determine the ***length*** of VNTR regions within the isolates' DNA. *van Belkum* does not sequence DNA and does not compare sequence data from a plurality of bacterial samples, as required by claim 1.

Specifically, *van Belkum* includes a section entitled "Materials and Methods," which describes the process he uses to analyze *H. influenzae* isolates. (*van Belkum*, p. 5018, col. 1.) In this section, *van Belkum* explains that "[p]ost-PCR gel electrophoresis was carried out . . . . Gels were . . . photographed with a charged-coupled device camera." (*id.* at p. 5018, col. 1, lines 65-68.) FIGS. 1 and 2 on pages 5021 and 5022, respectively, show the resulting gel electrophoresis photographs. These photographs compare the total length of selected DNA regions of various *H. influenzae* isolates, where the selected DNA regions are identified using primers.

As discussed in the Background section of Applicants' specification at pages 5-6, comparison of electrophoresis gel photographs suffers from a number of problems. For example, determining the lengths of each fragment in electrophoresis photographic images is subjective and not necessarily accurate. In contrast, the invention of claim 1 addresses these problems by comparing *sequence data* rather than electrophoresis gel photographs.

Although *van Belkum* does not disclose sequencing a VNTR region or comparing the sequence data for such a region, the Examiner nevertheless incorrectly argues that the claims do not require "comparing the nucleotide sequence of distinct 'cassettes' or 'repeat sequences' present in the variable number and arrangement within VNTR

regions of the pathogenic genome." (3/28/05 Final Office Action at p. 8, ¶ 18.) Applicants disagree. To the contrary, claim 1 specifically recites "sequencing a first region of deoxyribonucleic acid from each bacterium sample, *the first region consisting essentially of a variable number of tandem repeats (VNTRs) region*." Claim 1 also recites "comparing the sequenced data . . . of at least two of the plurality of samples *on both a base pair level and a repeat motif level.*" As explained above, a VNTR region is comprised of a variable number of adjacent (tandem) repeat sequences; *i.e.*, a variable number of adjacent, approximate copies of a pattern of nucleotides. Thus, contrary to the Examiner's argument, the claims specifically require sequencing and comparing the sequence data of a tandem series of repeats present in variable number (*i.e.*, a VNTR region).

Moreover, the Examiner acknowledges that "van Belkum et al. does not specifically describe the act of sequencing the H. influenzae isolate." (3/28/05 Final Office Action at p.8, ¶ 20.) Nevertheless, the Examiner appears to take the position that *van Belkum* inherently discloses DNA sequencing and comparison of sequence data, as recited in claim 1. Specifically, the Examiner attempts to rebut Applicants' arguments by asserting that "van Belkum et al. describes [that] the whole genome sequence as determined for H. influenzae (GenBank accession number L42023) was screen[ed] with a newly developed algorithm." (3/28/05 Final Office Action at p.8, ¶ 20.) The Examiner also argues that *van Belkum* "describes the result of the computer-aided searches identify[ing] all 23 potential VNTR loci comprising repeat units ranging from 2 to 6 bases in length and the TA repeat is present in H. influenzae AM20 and AM30 is not present in

the genome of the fimbria-deficient Rd strain" citing to page 5018, column 2 of *van Belkum*. (3/28/05 Final Office Action at p. 9, ¶ 21.)

Applicant's disagree with the Examiner's interpretation that the cited passages of *van Belkum* relate to sequencing and comparison of sequence data from a plurality of isolates, as required by claim 1. To the contrary, *van Belkum* screens one and only one whole genome GenBank DNA sequence for *H influenzae* **(sequence L42023) *for the purpose of creating primers to use in gel electrophoresis tests,*** not for the purpose of analyzing and comparing isolates. Specifically, *van Belkum* screens that single whole genome GenBank DNA sequence to look for regions with repeating sequences of nucleotides. Once such "potential VNTR loci" are found, (*van Belkum*, p. 5018, col. 2, ll. 4-6), *van Belkum* creates primers that identify the endpoints of these repeat regions. *See, e.g., van Belkum* at p. 5018, col. 1, lines 60-61 ("Twenty-nucleotide PCR primers were designed on the basis of sequences bordering the repetitive DNA."); *id.* at p. 5018, col. 2, lines 30-34 ("Primers for tracking repeat variability were designed for all of the potential VNTRs of H. influenzae (Table 2). The 20 nucleotide primers were selected on the basis of positional criteria only, their location being 5 nucleotides upstream and downstream of potential VNTRs.")

van Belkum next analyzes *H. influenzae* isolates by performing gel electrophoresis analysis using these primers that have been created. *See, e.g., van Belkum* at p. 5018, col. 2, lines 47-49 ("different DNA products were synthesized by using the primers designed for the amplification of the tetranucleotide repeats (Fig. 1).") This produces photographic gel images as shown in FIGS. 1 and 2 (pp. 5021 and 5022). (*See id.*, p. 5021, col. 1, ll. 4-7 ("Figure 2 displays the data obtained when DNAs

from the same, nonrelated strains were used for amplification with the primers specific for the repeats harboring units of 3, 5, or 6 nucleotides.") *van Belkum* also analyzes *H. influenzae* isolates by performing another type of gel electrophoresis analysis called "RAPD" which uses primers ERIC1 and ERIC2. (*See id.* at p. 5018, col. 1, lines 76-79 (describing RAPD analysis: "For the generation of the amplimer patterns, a combination of the primers ERIC1 and ERIC2 (42), in a single incubation mixture was employed. Amplification products were analyzed by electrophoresis on 1.5% agarose gels . . . and documented by Polariod photography.")

The gel electrophoresis photographs indicate only the ***length*** of repeat regions that have been isolated using the primers, not the actual sequence data in those repeat regions. Thus, *van Belkum* analyzes the length of repeat regions rather than comparing sequence data of a plurality of bacterial samples, as required by claim 1. *See, e.g., van Belkum* at p. 5018, col. 1, lines 71-72 ("The ***lengths*** of the PCR products were determined by comparison with small-molecular-size markers."); p. 5018, col. 2, lines 49-52 ("The average ***lengths*** of the repeats and the observed variation in *length* are given in Table 3. The variability in ***length*** of the repeats is quite high for this class of repeats."); p. 5019, col. 1, lines 4-6 ("Table 3 shows that changes in the ***size*** of a given repeat did not coincide with similar changes in other repeats."); p. 5019, col. 2, line 7 to p. 502, col. 1, line 1 ("All other VNTR regions showed fragment ***length*** variability. Five of the VNTR analyses provide clear ***length*** polymorphisms."); p. 5021, col. 2, lines 38-39 ("An overview of repeat ***length*** polymorphisms for the tetranucleotide repeats is provided in Table 5.")

van Belkum also states that "***[a]ll*** strains subjected to VNTR analyses of diverse kinds were ***characterized by RAPD***," (*id.* at p. 5018, lines 42-43), and that the RAPD analysis was performed by "analyz[ing] [amplification products] by ***electrophoresis*** on 1.5 % agarose gels . . . and documented by Polaroid photography." (*id.* at p. 5018, col. 1, line 78 to col. 2, line 1.) This further indicates that ***all*** strains were analyzed by RAPD gel electrophoresis and ***not*** by comparing sequence data as required by claim 1.

The Examiner also argues that *van Belkum* "describes the identification of VNTR sequences as directed to specific patients (Table 1)." This erroneously suggests that an actual nucleotide sequence is described. Table 1 does not describe any sequence data. Table 1 only lists a variety of strains identified by "RAPD type." And, as explained above, *van Belkum* specifically indicates that the RAPD type is identified by "analyz[ing] . . . electrophoresis on 1.5% agarose gels . . . and documented by Polaroid photography." (p. 5108, col. 1, line 78 to col. 2, line 1.) The gel photographs only indicate the length of the region identified by the primers and do not contain any indication of sequence data. Thus, Table 1 does not identify any sequence data.

In summary, *van Belkum* discloses comparison of gel electrophoresis photographs, not sequence data. Thus, *van Belkum* does not disclose "sequencing a first region of deoxyribonucleic acid from each bacterium sample, the first region consisting essentially of a variable number of tandem repeats (VNTRs) region", as recited in claim 1. Nor does *van Belkum* disclose "comparing the sequence data . . . of at least two of the plurality of samples," as recited in claim 1.

3. *Hoe*

The Examiner also attempts to cure the deficiencies in *Sloan* and *van Belkum* with *Hoe*. The Examiner, however, acknowledges that *Hoe* does not disclose VNTR regions. (3/28/05 Final Office Action at p. 10, ¶ 25). Instead, the Examiner states that "van Belkum et al. has been cited to describe VNTRs, not Hoe et al. as discussed below." (*Id.*) But as explained above, *van Belkum* does not disclose sequencing DNA or comparing sequence data from a plurality of bacterial samples, as required by claim 1. *van Belkum* merely compares the length of VNTR regions, which are indicated in gel electrophoresis photographic images (not sequence data). Thus, neither *Sloane*, nor *van Belkum*, nor *Hoe* discloses sequencing and comparing a VNTR region from a plurality of bacterium samples, as required by claim 1. For this reason alone, the Examiner's rejection is improper.

Hoe compares four methods of typing group A Streptococcus (GAS): (1) sequence analysis of the *emm* gene, (*Hoe*, p. 255, col. 2 to p. 256, col. 1); (2) sequence analysis of the *sic* gene, (*id.*, p. 256, col. 1 to p. 257, col. 1); (3) RFLP analysis (similar to electrophoresis), (*id.*, p. 257, col. 1 to p. 259, col. 1); and (4) spacer oligotyping (spoligotyping) of a region with "direct repeat" (DR) units. (*id.*, p. 259, col. 1 to p. 260, col. 1).

The Examiner cites to the fourth method, the "spacer oligotyping" method, because it involves analyzing a DNA region with direct repeat (DR) units. (*See* 3/28/05 Final Office Action at p.4, ¶ 10, p. 15, ¶ 44.) *Hoe's* spacer oligotyping method, however, identifies a bacterial species by analyzing the "spacer regions"—the sequences between DR units—rather than the repeat units themselves. (*See Hoe*, p.

259, col. 2 & p. 260, Figure 4 .) Specifically, *Hoe* looks at a region of the GAS chromosome that consists of seven DR elements separated by six unique 30-base pair spacer regions. (*Hoe*, p. 259, col. 1, ll. 33-39.) Figure 4 of *Hoe* (p. 260) shows a spacer oligotyping analysis of the various differences in the spacer regions between individual DR (direct repeat) elements. As shown in the figure, the sequence within DR elements is identical in all cases (the final element called DR' has four nucleotide changes from the DR units.) *Hoe* differentiates the different isolates based on analysis of the spacer regions *between* the DR units, not based on an analysis of the sequence data *within* the repeats.

For example, Figure 4 shows that the first isolate, "DR type 2.0," is comprised of a DR unit followed by a spacer region of type 2, followed by another identical DR unit, followed by a spacer region of type 8. The second isolate, "DR type 2.1," consists of a DR unit followed by a spacer region of type 2, followed by another identical DR unit, followed by a spacer region of type 6. The third isolate, "DR type 2.2," consists of a DR unit followed by a spacer region of type 6, followed by another identical DR unit, followed by a spacer region of type 8. *Hoe* thus differentiates the different isolates by analyzing the variations in spacer regions between the identical DR units. Because *Hoe*'s spacer oligotyping method differentiates the isolates based on an analysis of *the spacer regions* between DR elements, *Hoe* teaches away from the analysis of the DR nucleotide sequence *within* a series of adjacent (tandem) repeat sequences (*i.e.*, a VNTR region), as required by claim 1.

Thus, in summary, none of *Sloane*, *van Belkum*, or *Hoe* discloses sequencing a VNTR region or comparing the sequence data from such a region to perform tracking of

the spread of bacteria. *Sloane* does not even mention bacteria or DNA. *van Belkum* does not perform sequencing or compare sequence data but uses gel electrophoresis photographs to indicate the length of a VNTR region. *Hoe* analyzes the spacer regions between direct repeat units. Thus, because none of these references discloses sequencing a VNTR region, the Examiner has failed to establish a *prima facie* case of obviousness.

B. Neither *Hoe*, *Sloane*, nor *van Belkum* Discloses Comparing Sequence Data on Both a Base Pair Level and Repeat Motif Level, as Required by Claims 1, 32 and 33

Neither *Sloane*, nor *van Belkum*, nor *Hoe* discloses "comparing the sequence data stored in the database of at least two of the plurality of samples on both a base pair level and a repeat motif level" as recited in independent claims 1, 32 and 33. As described in the Applicants' specification, the method of the claimed invention compares DNA sequence data "on the repeat motif level" by comparing the similarity of the repeat motifs (*i.e.*, the pattern of cassettes) in each strand of DNA. (Applicants' specification at p. 8, ll. 22-23; p. 24, ll. 19-21; p. 31, l. 20 to p. 32, l. 4; p. 34, l. 13 to p. 35, l. 11; FIG. 3 (Step 308); FIG. 5.) The method of the present invention compares DNA sequence data on the base pair level by comparing the similarity of the individual sequences of base-pairs (*i.e.*, A's, G's, C's, and T's) in each piece of DNA. (Applicants' specification at p. 32, ll. 8-11; FIG. 3 (Step 310).) Pages 32-33 of Applicants' specification provides an exemplary equation and method for calculating a cost (a measure of phylogenetic relatedness) based on both a comparison of the similarity at the repeat motif level and the similarity at the base pair level:

$$\text{Relatedness } R = W_{dbp}D_{bp} + W_{ibp}I_{bp} + W_{drep}D_{drep} + W_{irep}I_{rep} + W_{irep}I_{rep}$$

(Applicants' specification at p. 33.)

The Examiner incorrectly argues that *van Belkum* discloses the claim element of "comparing . . . on both a base pair level and a repeat motif level." (3/28/05 Final Office Action at p. 11, ¶ 26.) According to the Examiner, "van Belkum et al. describes the result of the computer-aided searches identify[ing] all 23 potential VNTR loci comprising repeat units ranging from 2 to 6 bases in length and the TA repeat is present in H. influenzae AM20 and AM30 is not present in the genome of fibria-deficient RD strain." (*Id.*, citing to page 5018, col. 2 of *van Belkum*). Applicants disagree with the Examiner's interpretation. In the portion of *van Belkum* referenced by the Examiner, *van Belkum* describes searching one and only one entire *H. influenzae* genome for areas with repeat units, *i.e.* "potential VNTR loci". Once these "potential VNTR loci" are identified, *van Belkum* creates primers to allow the *H. influenzae* isolates to be analyzed by gel electrophoresis, as described above.

Analyzing a single genome sequence to look for repeats is not "comparing the sequence data stored in the database of at least two of the plurality of samples on both a base pair level and a repeat motif level" as recited in claim 1. Neither is this claim limitation disclosed in *Sloane* or *Hoe*. Thus, because none of *Sloane*, *Hoe*, or *van Belkum*, alone or in combination, teach or suggest this claim element recited in claim 1, Appellants submit the Examiner has not established a *prima facie* case of obviousness.

C. There is No Motivation to Combine *Hoe's* Spacer Oligotyping Method With *Van Belkum's* Gel Electrophoresis Photograph Analysis of VNTR Region Length

The Examiner's rejection fails because one of skill in the art would not have been motivated to combine *Hoe's* analysis of spacer regions (spacer oligotyping) with *van*

Belkum's analysis of gel electrophoresis photographs indicating VNTR region length. As mentioned above, the Examiner acknowledges that *Hoe* does not disclose VNTR regions. (3/28/05 Final Office Action at p. 10, ¶ 25.) Because *Hoe* analyzes the spacer regions between the DR elements to identify the isolate (*i.e.*, spacer oligotyping), *Hoe* teaches away from the claimed invention which analyzes the sequence data within a VNTR region, which is a series of adjacent (tandem) repeat sequences. In other words, the invention of claim 1 sequences and compares DNA sequence data within a series of tandem repeat sequences, which is neither taught nor suggested by *Hoe*.

The Examiner incorrectly argues that one of ordinary skill in the art would be motivated to combine *Hoe* and *van Belkum* because, according to the Examiner, *van Belkum* "does contain interspersed unique spacer regions" and the Examiner cites to Table 2. (3/28/05 Final Office Action at p.4, ¶ 10.) The Examiner essentially argues that because *van Belkum* looks at different VNTR regions in the chromosome, the chromosome must inherently have spacer regions, which the Examiner argues are the regions between the VNTR regions. (*Id.*) The Examiner's analysis is incorrect because *van Belkum* simply ignores the non-VNTR regions. *van Belkum i*dentifies the strain of the *H. influenzae* isolate only by analyzing the lengths of the VNTR regions (as shown the gel photographs) and does not consider other non-VNTR regions. The fact that the chromosome includes non-VNTR regions is irrelevant because those regions are not analyzed. Thus, one of ordinary skill in the art would not be motivated to combine *Hoe*, which teaches spacer oligotyping (analysis of spacer regions), with *van Belkum*, which teaches gel electrophoresis photograph analysis of VNTR region length.

The Examiner also alleges that one would be motivated to combine the spacer oligotyping method of *Hoe* with the VNTR-electrophoresis analysis of *van Belkum* because "Sloane provides the motivation to combine the teaching from all three references." (3/28/05 Final Office Action, p.4, ¶ 9.) But *Sloane* does not mention sequencing or even DNA, let alone analysis of VNTR regions. Thus, *Sloane* does not provide motivation to combine the disparate teachings of *Hoe* and *van Belkum*. Rather, the Examiner improperly uses the Applicants' own specification as a blueprint for piecing together various pieces of *Sloane*, *Hoe*, and *van Belkum*.

The Examiner also incorrectly states that "[t]he method of Hoe et al. comprises sequencing the sic gene wherein a region contains repeat sequences to unambiguously differentiate 30 M1 isolates." (3/28/05 Final Office Action at p. 13, ¶ 35.) *Hoe* does not disclose sequencing a repeat region in either the *sic* or *emm* genes. The only repeat sequences disclosed in *Hoe* are the DR units, which are not in the *sic* or *emm* genes. As discussed above, *Hoe's* spacer oligotyping method analyzes the spacer regions between the DR units. Thus, *Hoe* only discloses analyzing genes without repeats (*emm* and *sic* genes) and analyzing the spacers within the DR regions. Accordingly, *Hoe* teaches away from analyzing the sequence data within a series of tandem repeats (*i.e.*, within a VNTR region, as recited in the claims).

Furthermore, *Hoe* concludes that spacer oligotyping of the DR region proved to be a less effective typing method than analysis of the *sic* gene. (*Hoe*, p. 261, col. 1, ll. 19-22.) *Hoe* also concludes that spacer oligotyping of the DR region in GAS is less useful than spacer oligotyping for *M. tuberculosis* because of the lack of distinct spacer regions in GAS, which only has 13 distinct spacer regions. (*Id.*, col. 1, ll. 22-33.) Thus,

Hoe is concerned with variability in the number of spacer regions not tandem repeat sequences. *Hoe* thus further teaches away from analysis of a VNTR region, a region with a series of tandem repeats.

D. There is no Motivation to Combine *Sloane's* Patient Diagnosis System with *Hoe's* Spacer Oligotyping Method or *Van Belkum's* Gel Electrophoresis Photograph Analysis

The Examiner has also failed to establish a *prima facie* case of obviousness because one of ordinary skill in the art would not have been motivated to combine *Sloane's* patient diagnosis system with *Hoe's* spacer oligotyping method or *van Belkum's* analysis of gel electrophoresis photographs. As discussed above, *Sloane* is directed to a system for diagnosing and treating patients. *Sloane* does not mention or suggest sequencing or DNA analysis. *Sloane* never even mentions DNA. Nor does *Sloane* disclose tracking the spread of bacteria over time, as recited in independent claims 1, 32 and 33.

The Examiner argues that *Sloane* discloses "identifying and tracking epidemiological events and/or trends (outbreak)" citing to the Abstract and column 1, line 39 to column 2, line 12. (3/28/05 Final Office Action at p. 11, § 27.) The epidemiological database feature disclosed by *Sloane*, however, is directed towards diagnosing a patient, not to tracking the spread of bacteria over time or controlling the spread of bacteria, as recited in independent claims 1, 32 and 33. For example, *Sloane* explains that "if a food poisoning epidemic breaks out in a particular locale, the epidemiological database computer facility . . . is in a position to return an electronic message to an e-doc submitting . . . a suggestion that food poisoning be considered as a likely source of the patient's problems." (Col. 2, ll. 30-38.)

At best, *Sloane* discloses that the CDC can identify if there are a number of similar diagnoses such as food poisoning in the same geographical location. (*Sloane*, col. 8, lines 2-18.) But *Sloane* does not disclose tracking the spread of bacteria or performing any type of analysis that would allow the bacterial spread to be tracked. In contrast, the claimed invention relies on the mutating characteristics of bacterial DNA that allows for the spread of bacteria to be tracked over time.

Thus, one of skill in the art would not have been motivated to combine *Sloane's* patient diagnosis system with either *van Belkum's* method of analyzing gel electrophoresis photographs or *Hoe's* spacer oligotyping method.

Claim 16

E. Neither *Sloane*, nor *Hoe*, nor *van Belkum* Disclose Treating the Insertion or Deletion of a Repeat Sequence as a Single Genetic Event as Recited in Claim 16

Claim 16 is dependent on claim 1, and is thus allowable for all the reasons recited above with respect to independent claim 1. Additionally, claim 16 is further allowable because none of the cited references discloses or suggests "treating the insertion or deletion of a repeat sequence as a single genetic event," as recited in claim 16. As described on page 31 of Applicants' specification, "[t]he software of the present invention recognizes the insertion or a deletion of single 24 base-pair length cassette as a single event, rather than 24 separate events." (p. 31, lines 5-6). Thus, when determining the phylogenetic relatedness of two bacterium samples, the invention treats the insertion or deletion of a repeat sequence (cassette) as a single genetic event. (*See* Applicants' specification at pp. 31, lines 4-23; p. 35, lines 7-8.)

In response, the Examiner argues that "Hoe et al. describes each allele is characterized by single nucleotide changes resulting in single amino acid substitutions in the resulting M1 protein (page 256, column 1, lines 12-15) and eight new nucleotide substitutions were identified in eight codons, and one codon had a new nucleotide change (sequence)(page 257, column 1, lines 14-21), as in instant claim 16." (3/28/05 Final Office Action at p. 17, ¶ 52.)

The Examiner misses the point. Claim 16 requires treating an insertion or deletion of a *repeat sequence* as a single genetic event, rather than treating it as a number of genetic events corresponding to the number of nucleotides inserted or deleted that constitute the repeat sequence. The portions of *Hoe* cited by the Examiner merely note that various alleles are characterized by individual nucleotide changes. None of the cited portions of *Hoe* relate to insertions or deletions of repeat sequences. Nor does *Hoe* anywhere disclose or suggest that the insertion or deletion of a repeat sequence should be treated as a single genetic event. Thus, the Examiner's rejection of claim 16 is improper and should be reversed.

The Rejections of Claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44 Under 35 U.S.C. § 103(a) Over the Combination of *Sloane*, *van Belkum*, *Hoe*, *O'Brien*, and *Paradiso* Should Be Reversed

The Examiner alleges that *O'Brien* and *Paradiso* disclose various elements recited in dependent claims 8, 10, 11, 22, 23, 24, 35, and 38 that are not present in *Sloane*, *van Belkum*, and *Hoe*. (*See* 3/28/05 Final Office Action at pp. 18-19, ¶ ¶ 54-60.) The Examiner, however, does not allege that *O'Brien* or *Paradiso* contributes to the rejection of independent claims 1, 32, and 33 or dependent claim 16 or that *O'Brien* and/or *Paradiso cure the deficiencies of Sloane*, *van Belkum*, and *Hoe*. (*See id.*) In any

event, Appellant submits respectfully that *O'Brien* and *Paradiso* do not in fact cure any of the above-described deficiencies of *Sloane*, *Hoe*, and *van Belkum* with respect to independent claims 1, 32, or 33 or dependent claim 16. Neither *Paradiso* nor *O'Brien* discloses sequencing of VNTR regions, the comparison of VNTR sequence data stored in a database of at least two of a plurality of samples on both a base pair level and a motif level, or treating the insertion or deletion of a repeat sequence as a single genetic event.

Thus, Appellants respectfully submit that the Board should reverse the rejection of independent claims 1, 32, and 33 and dependent claim 16 under 35 U.S.C. § 103(a). Furthermore, the rejection of dependent claims 8, 10, 11, 22, 23, 24, 35, and 38 should be reversed for at least the reasons argued above with respect to the independent claims.

VIII. Conclusion

For the reasons given above, pending claims 1, 3-5, 7, 8, 10-14, 16, 17, 21-36, 38 and 44 are allowable and reversal of the Examiner's rejection is respectfully requested.

To the extent that any additional extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 that are not enclosed herewith, including any additional fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 19-5127 (Order No. 19124.0002).

Respectfully submitted,

Swidler Berlin LLP

Dated: November 28, 2005

By: _____
Robert R. Seabold, Ph.D.
Registration No. 41,298
(202) 295-8466

Swidler Berlin LLP
3000 K St, NW, Suite 300
Washington DC 20007
Telephone: (202) 424-7500
Facsimile: (202) 295-8478

Appendix A: Listing of Claims Under Rule 41.37(c)(1)(viii)

1. A method of tracking spread of infectious bacteria, comprising:

obtaining a plurality of bacterium samples from a plurality of patients or objects at a plurality of different physical locations;

sequencing a first region of deoxyribonucleic acid from each bacterium sample, the first region consisting essentially of a variable number of tandem repeats (VNTRs) region;

storing in a database for each of the plurality of bacterium samples: a) the sequence data from the first sequenced region of each bacterium sample, and b) a physical location of the patient or object from which each bacterium sample was obtained;

comparing the sequence data stored in the database of at least two of the plurality of samples on both a base pair level and a repeat motif level;

determining a measure of phylogenetic relatedness between the compared samples based upon differences between the compared sequence data;

identifying patients infected or objects contaminated with phylogenetically related bacteria based on the phylogenetic relatedness determination;

tracking the spread over time of the bacteria based on: a) the identified patients or contaminated objects, and b) the physical locations of the identified patients or objects stored in the database; and

providing a warning based on the tracking of the spread of the bacteria wherein the warning allows the recipient of the warning to control the further spread of the bacteria.

2. (Canceled)

3. The method of claim 1, wherein the database is a centralized database located remote from where the sample is obtained.

4. The method of claim 1, wherein the database is located in the same location as where the sample is obtained.

5. The method of claim 1, wherein the first region that is sequenced is a region having a mutation rate sufficient to differentiate between subspecies to determine phylogenetic relatedness and to track the bacteria.

6. (Canceled)

7. The method of claim 6, wherein the bacterium is *Staphylococcus aureus* and the first region is located in the protein A gene or the coagulase gene.

8. The method of claim 7, wherein each bacterium sample is obtained from a patient as the patient is admitted to a health care facility and prior to being exposed to patients in the health care facility.

9. (Canceled)

10. The method of claim 1, further including:

obtaining a medical history from a patient from which at least one of the plurality of bacterium samples was taken;

determining an infection risk factor based on the patient's medical history, the infection risk factor being a measure of the patient's risk of acquiring an infection; and

taking appropriate infection control measures in accordance with the infection risk factor.

11. The method of claim 10, further including:

transmitting the patient's medical history to the database without transmitting private patient information; and

storing the private patient information in a local database at the remote from the database that the patient's medical history is transmitted to.

12. The method of claim 1, wherein the step of sequencing comprises either:

a) sequencing the first region at a remote facility and transmitting the resulting sequence data to the database via a computer network; or

b) sending each of the plurality of bacterium samples to an infection control facility associated with the database, sequencing the first region at the infection control facility, and storing the sequence data in the database.

13. The method of claim 1, wherein the first region is identified by a set of primers.

14. The method of claim 1, wherein the first region is amplified prior to sequencing.

15. (Canceled)

16. The method of claim 1, wherein the step of determining the phylogenetic relatedness between the compared samples includes:

identifying repeat sequences in the sequence data for each of the compared samples; and

treating the insertion or deletion of a repeat sequence as a single genetic event.

17. The method of claim 16, wherein determining the phylogenetic relatedness between the compared samples further including:

treating an insertion or deletion of an individual nucleotide as a single genetic event.

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. The method of claim 1, wherein the step of determining the phylogenetic relatedness between the compared samples includes at least one of:

comparing a first bacterium sample to other samples obtained from the same facility as where the first bacterium sample was taken, thereby determining a local phylogenetic relatedness;

comparing the first bacterium sample other samples obtained from the same geographical region as where the first bacterium sample was taken, thereby determining a regional phylogenetic relatedness; and

comparing the first bacterium sample other samples obtained globally, thereby determining a global phylogenetic relatedness.

22. The method of claim 1, wherein the steps of storing in a database and tracking the spread of the infection further comprises:

transmitting over a computer network from a remote facility to an infection control server the sequence data from the first sequenced region of each of the plurality of bacterium samples and the physical location of the patient or object from which each bacterium sample is taken.

23. The method of claim 22, further including:

storing a map of the physical location of where the plurality of samples were obtained in the database; and

determining the spread of the infection based on the map.

24. The method of claim 23, further including:

sensing the patient's physical location prior to transmitting the patient's physical location.

25. The method of claim 1, further including:

determining the virulence of the bacterium by retrieving the virulence data of identical or similar bacteria from the database; and

transmitting over a computer network virulence information to a location where the bacterium sample was obtained.

26. The method of claim 1, further comprising:

determining drug resistance and treatment information of the bacterium by retrieving drug information data of identical or similar bacteria from the database; and

transmitting over a computer network the drug information data to a location where the bacterium sample was obtained.

27. The method of claim 1, wherein providing a warning includes:

determining whether a location where each bacterium was obtained has an outbreak problem; and

transmitting over a computer network an outbreak warning to each location having an outbreak problem.

28. The method of claim 1, further including:

sequencing a second region of the nucleic acid of each bacterium sample;

storing the sequence data from the second region of the nucleic acid of each bacterium sample in a database;

comparing the second sequenced region of at least two of the plurality of samples, wherein the determining a measure of phylogenetic relatedness comprises; and

determining a measure of phylogenetic relatedness based on the comparison of the first and second sequenced regions.

29. The method of claim 28, wherein the determination of relatedness based on the second sequenced region is used to verify the determination of relatedness based on the first sequenced region.

30. The method of claim 28, further including:

identifying a first level of subspecies of each bacterium sample based on the first sequenced region; and

identifying a second level of subspecies of each bacterium sample based on the second sequenced region.

31. The method of claim 28, further including:

tracking the global spread of an infection based on sequencing and comparing a slowly mutating region of the nucleic acid; and

tracking the local spread of an infection based on sequencing and comparing a more rapidly mutating region of the nucleic acid.

32. A system for tracking spread of infectious bacteria, comprising:

a computer network;

a centralized database;

a remote facility connected to the computer network, the remote facility obtaining a plurality of bacterium samples from a plurality of patients or objects at a plurality of different locations;

a server connected to the computer network, the server receiving sequence data for a first sequenced region of a nucleic acid from each of the plurality of bacterium samples and a physical location of a patient or object from which each bacterium sample was obtained, the first sequenced region comprising consisting essentially of a variable number of tandem repeats (VNTRs) region;

storing in a database for each of the plurality of bacterium samples: a) the sequence data from each of the plurality of bacterium samples, and b) the physical location of the patient or object from which each bacterium sample was obtained;

accessing the centralized database and comparing the stored sequence data of at least two of the plurality of bacterium samples on both a base pair level and a repeat motif level;

determining a measure of phylogenetic relatedness between the compared samples;

identifying patients infected or objects contaminated with phylogenetically related bacteria based on the phylogenetic relatedness determination;

tracking the spread over time of the bacteria based on a) the identified patients or objects, and b) and the physical locations of the identified patients or objects stored in the database; and

transmitting a warning over the computer network to the remote facility based on the tracking of the spread of the bacteria, thereby allowing the remote facility to control the further spread of the bacterial infection.

33. Computer executable software code stored on a computer readable medium, for performing a method of tracking spread of infectious bacteria over a computer network, comprising:

obtaining a plurality of bacterium samples from a plurality of patients at a plurality of different locations;

sequencing a first region of a nucleic acid from each of the pluralility of bacterium samples, the first region consisting essentially of a variable number of tandem repeats (VNTRs) region;

storing in a database: a) the sequence data from the first sequenced region of each bacterium sample, and b) a physical location of a patient or object from which each bacterium sample was obtained;

comparing the stored sequence data of at least two of the plurality of samples on both a base pair level and a repeat motif level;

determining a measure of phylogenetic relatedness between the compared samples;

identifying patients infected or objects contaminated with phylogenetically related bacteria based on the phylogenetic relatedness determination;

tracking the spread of the bacteria based on the identified patients or objects and the physical locations of the identified patients and objects stored in the database; and

providing bacterial spread information based on the tracking of the spread of the bacteria, thereby allowing use of the bacterial spread information to further control the spread of the bacteria.

34. The method of claim 1, wherein the plurality of bacterium samples are obtained at a facility remote from where the sequencing is carried out.

35. The method of claim 34, wherein the remote facility is a health care facility, and the sample of the bacterium is obtained from a patient as the patient is admitted to a health care facility and prior to being exposed to patients in the health care facility.

36. The method of claim 1, wherein the sample is obtained at a facility remote from where the sequencing, comparing and determination of a measure of phylogenetic relatedness are carried out.

37. (Canceled)

38. The method according to claim 1, wherein infected patients are identified prior to an outbreak of the bacterial infection.

39. (Canceled)

40. (Canceled)

41. (Canceled)

42. (Withdrawn)

43. (Withdrawn)

44. The system of claim 32, further comprising:

sequencing the first region of the nucleic acid for each of the plurality of bacterium samples at the remote facility; and

transmitting the sequence data to the server over a computer network.

Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

There is no evidence being relied upon by Appellants in this appeal.

Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

There are currently no other appeals or interferences, of which Appellants, Appellants' legal representative, or Assignee are aware, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.